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Synthesis and Fungicidal Activity of *N*-(*p*-Sulfonylphenyl)-N^1-Carbamoylureas

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Abstract: A series of 11 *N*-(*p*-sulfonylphenyl)-N^1-carbamoylureas was prepared by reaction of 1,6-diphenyl-2,4-dioxohexahydro-*s*-triazine with chlorosulfonic acid and thionyl chloride. The resultant *N*-(*p*-chlorosulfonylphenyl)-N^1-carbamoylurea was subsequently condensed with amines, butanol, hydrazine and sodium azide. The hydrazide was reacted with carbonyl compounds and the azide with trimethyl phosphite. The products were tested for in-vivo fungicidal activity against barley powdery mildew (*Erysiphe graminis*); the acetone hydrazone derivative showed the highest activity. © 1998 SCI.

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Key words: fungicides; barley powdery mildew; sulfonylphenylcarbamoylureas

1 INTRODUCTION

Arylureas are well established soil-acting herbicides,[1] while sulfonylureas are remarkably potent selective herbicides for control of broad-leaved weeds in cereals.[1] In addition, certain sulfonamides possess weak systemic antifungal activity;[1] however, there are no reports of the biological activity of the class of *N*-sulfonylphenylcarbamoylureas described in this paper.

2 EXPERIMENTAL METHODS

2.1 General experimental procedures

Melting points are uncorrected. IR spectra were obtained as nujol mulls. [^{1}H] and [^{13}C]NMR spectra were recorded at 250 MHz and 67 MHz respectively in dimethyl sulfoxide (DMSO) solution unless otherwise stated; an asterisk indicates a resonance reduced by D_2O treatment. All solvents used were HPLC grade and were not further purified. All yields reported are isolated yields of material judged to be homogenous by TLC. Elemental analysis (C,H,N) of all compounds was within $\pm 0{\cdot}4\%$ of the theoretical values.

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2.2 Synthesis of *N*-(*p*-sulfonylphenyl)-N^1-carbamoylureas

The synthesis of the *N*-(*p*-sulfonylphenyl)-N^1-carbamoylureas prepared in this study is outlined in Fig. 1.

Benzylideneaniline (**1**, Fig. 1) was reacted with chlorosulfonylisocyanate (CSI) as described by Suschitzky *et al.*[2,3] to give 3,5-dichlorosulfonyl-1,6-diphenyl-2,4-dioxohexahydro-*s*-triazine (**2**) which, with potassium iodide, was converted into 1,6-diphenyl-2,4-dioxohexahydro-*s*-triazine (**3**). The latter, by reaction with excess chlorosulfonic acid in thionyl chloride, afforded *N*-(*p*-chlorosulfonylphenyl)-N^1-carbamoylurea (**4**); this was a novel ring-opening reaction recently discovered in these laboratories.[4]

The sulfonyl chloride (**4**) by condensation with ammonia, amines, *n*-butanol and hydrazine gave the corresponding sulfonyl derivatives (**5a**–**f**) (Table 1). The

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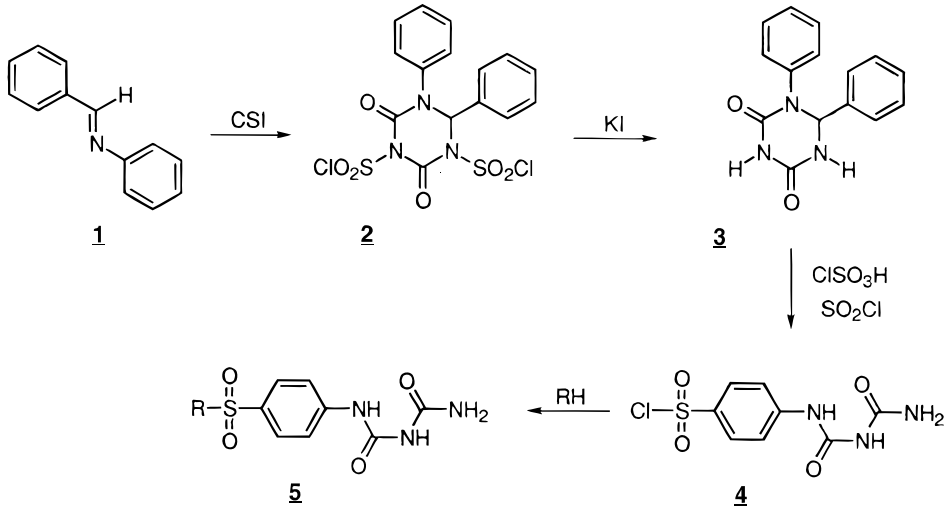
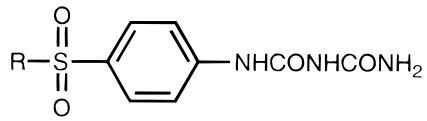
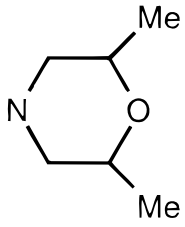


Fig. 1. General route for synthesis of *N*-(*p*-sulfonylphenyl)-N^1-carbamoylureas.

sulfonyl hydrazide (**5f**) was further condensed with acetone, acetaldehyde, butan-2-one and benzaldehyde to yield the hydrazones (**5g–j**) (Table 1). The sulfonyl chloride (**4**) was also reacted with sodium azide to give the sulfonyl azide (**5k**) which on warming with trimethyl phosphite afforded the trimethylphosphatimine (**5l**) (Table 1). The sulfonyl derivatives were obtained in variable yields (42–91%).

TABLE 1
Antifungal Activity of *N*-(*p*-Sulfonylphenyl)-N^1-Carbamoylureas in Comparison with Propiconazole and Fenpropidin

5 

Compound No.	*R*	*Leaf Area Infection* (%) *Time* (*days*) 6	7	8	10	12
5a	NH_2	34		46	36	
5b	NHEt		63		64	
5c	NEt_2		60		45	36
5d		83		79	77	
5e	$O(CH_2)_3Me$	77		79	47	
5f	NH-NH_2		83		79	74
5g	NHN=CMe_2	95		94	91	
5h	NHN=CHMe	57	52			
5i	NHN=C(Me)Et	63	48			
5j	NHN=CHPh	70	66			
5k	N_3	(Not Tested)				
5l	N=$P(OMe)_3$	32		24		
	Propiconazole	88		90	87	
	Fenpropidin	81		86	83	

2.2.1 3,5-Dichlorosulfonyl-1,6-diphenyl2,4-ioxohexahydro-s-*triazine* (***2***)
A solution of *N*-benzylideneaniline (**1**, 15 g, 83 mmol) in dichloromethane (15 ml) was added dropwise to a stirred solution of chlorosulfonylisocyanate (18 ml, 0·207 mol) in dichloromethane (15 ml). The temperature was maintained at 10°C by cooling (ice bath) while diethyl ether (50 ml) was gradually added, and the mixture left in the ice bath for 15 min. The resultant solid was filtered off, washed with ether and dried (vacuum desiccator) giving 28·4 g (74%) as a white powder, m.p. 96–97°C (lit[3] 95°C): IR υ_{max} 1790, 1770, 1370, 1150 cm^{-1}; [^{1}H]NMR δ 7·4–7·1 (m, 10H); EI/MS *m/z*: 365 (M-SO_2Cl).

2.2.2 1,6-Diphenyl-2,4-dioxohexahydro-s-*triazine* (***3***)
Compound **2** (3·5 g, 7·5 mmol) was gradually added to methanol (20 ml) containing aqueous potassium iodide (40 g $litre^{-1}$; 10 ml). During the reaction, the pH of the mixture was maintained at 1–3 by addition of potassium hydroxide solution (200 g $litre^{-1}$), and at the end of the addition the pH was adjusted to 7. The resultant precipitate was filtered off, recrystallised from methanol and dried giving 1·8 g (90%), m.p. 254–256°C: IR υ_{max} 3300, 1790, 1770; [^{1}H]NMR ($CDCl_3$) δ 10·1*, 8·7* (2 × s, 2H), 7·4–7·1 (m, 10H), 6·0 (s, 1H); [^{13}C]NMR δ 152, 150, 139–126 (6 signals); EI/MS *m/z*: 267 (M^+).

2.2.3 N-(p-*Chlorosulfonylphenyl*)-N^1-*carbamoylurea* (***4***)
Compound **3** (5 g, 18 mmol) was added portionwise to a mixture of chlorosulfonic acid (13 g, 0·112 mol) and thionyl chloride (20 ml). The solution was left at room temperature for three days and poured on to ice-water (250 ml). The precipitate was filtered off to give 3·2 g (64%), m.p. 185–187°C: IR υ_{max} 3300, 1340, 1160 cm^{-1}; [^{1}H]NMR δ 10·2*, 9·1* (2 × s, 2H), 7·7–7·4 (m, 4H), 7·2* (br s, 2H); EI/MS *m/z*: 217 (M-$NHCONH_2$).

2.2.4 General procedure for the preparation of N-(p-*sulfamoylphenyl*)-N^1-*carbamoylureas* (***5a–5d***)
A solution of compound **4** (1·5 g, 5·4 mmol) was treated dropwise with either an excess of aqueous ammonia solution (0·880) or an ethanolic solution of the appropriate amine (0·75 mol). The mixture was stirred at room temperature for 3 h and poured on to an ice-water mixture (100 ml); concentrated hydrochloric acid (~five drops) was added to bring the mixture to pH 7. The precipitate was filtered off, washed with water (25 ml) and purified by recrystallisation from ethanol to give the desired sulfonamide derivative.

2.2.4.1 N-(p-*Sulfamoylphenyl*)-N^1-*carbamoylurea* (***5a***). Prepared using ammonia, 46% yield of a white solid, m.p. 192–193°C; IR υ_{max} 3400, 3320, 1340, 1160 cm^{-1}; [^{1}H]NMR δ 10·2*, 9·1* (2 × s, 2H), 7·8–7·6 (m, 4H), 7·2* (br s, 2H), 7·0* (br s, 2H); [^{13}C]NMR δ 155·2, 151·8, 141·1, 138·0, 126·7, 118·4; FAB (+)/MS *m/z*: 259 ($M^+ + 1$).

2.2.4.2 N-(p-*Ethylsulfamoylphenyl*)-N^1-*carbamoylurea* (***5b***). Prepared using ethylamine, 54% yield of a white solid, m.p. 188–189°C; IR υ_{max} 3300, 1340, 1160 cm^{-1}; [^{1}H]NMR δ 10·2*, 9·1* (2 × s, 2H), 7·8–7·6 (m, 4H), 7·2* (s, 1H), 7·0* (br s, 2H), 2·7 (q, 2H), 1·0 (t, 3H); [^{13}C]NMR δ 155·2, 151·8, 141·6, 134·2, 127·7, 118·6, 14·6; EI/MS *m/z*: 226 (M-$NHCONH_2$).

2.2.4.3 N-(p-N,N-*Diethylsulfamoylphenyl*)-N^1-*carbamoylurea* (***5c***). Prepared using diethylamine, 49% yield of white crystals, m.p. 187–188°C; [^{1}H]NMR δ 10·2*, 9·1* (2 × s, 2H), 7·8–7·6 (m, 4H) 7·0* (br s, 2H), 3·2 (q, 4H), 1·1 (t, 6H); [^{13}C]NMR δ 155·2, 151·8, 141·9, 130·3, 127·9, 118·7, 13·9; EI/MS *m/z*: 254 (M-$NHCONH_2$); FAB (+)/MS *m/z*: 315 ($M^+ + 1$).

2.2.4.4 N-(p-*2,6-Dimethylmorpholinosulfonylphenyl*)-N^1-*carbamoylurea* (***5d***). Prepared using 2,6-dimethylmorpholine, 52% yield of white crystals, m.p. 182–184°C; [^{1}H]NMR δ 10·2*, 9·1* (2 × s, 2H), 7·8–7·6 (m, 4H), 7·0* (br s, 2H), 3·4–3·0 (m, 4H), 2·2 (t, 2H) 1·0 (s, 6H); EI/MS *m/z*: 296 (M-$NHCONH_2$).

2.2.4.5 N-(p-*Butoxysulfonylphenyl*)-N^1-*carbamoylurea* (***5e***). A solution of *n*-butanol (0·4 g, 5·5 mmol) in pyridine (1·7 g, 22 mmol) was cooled $<20°$. To this solution, compound **4** (1·53 g, 5·5 mmol) was added portionwise with stirring. After 3 h, the mixture was acidified with cold concentrated hydrochloric acid; the precipitate was filtered off, washed and dried giving 0·56 g (42%) as a white powder, m.p. 184–185°C; [^{1}H]NMR δ 10·4*, 9·1* (2 × s, 2H), 7·8–7·6 (m, 4H), 7·0* (br s, 2H), 4·0–1·3 (m, 6H), 0·8 (t, 3H); [^{13}C]NMR δ 155·3, 151·8, 143·3, 138·2, 128·9, 118·8, 70·4, 30·1, 18·0, 13·1; EI/MS *m/z*: 255 (M-$NHCONH_2$).

2.2.4.6 N-(p-*Hydrazinosulfonylphenyl*)-N^1-*carbamoylurea* (***5f***). Compound **4** (2 g, 7·2 mmol) was treated with 98% hydrazine hydrate (1·45 g, 28 mmol) in methanol (25 ml). The reaction was carried out initially at 0°C and then at room temperature for 3 h. The mixture was poured on to crushed ice/water (200 ml) and the precipitate collected by filtration, washed with water, and dried giving 1·9 g (90%) as a white powder. m.p. 176–177°C; [^{1}H]NMR δ 10·3*, 8·2* (2 × s, 2H) 7·8–7·6 (m, 4H), 7·0* (br s, 2H), 4·0* (br s, 2H); [^{13}C]NMR δ 155·2, 151·8, 141·9, 131·5, 128·8, 118·4; EI/MS *m/z*: 213 (M-$NHNH_2$).

2.2.4.7 N-(p-*Isopropylidenehydrazinosulfonylphenyl*)-N^1-*carbamoylurea* (***5g***). Compound **5f** (1·9 g, 6·9 mmol) was added to acetone (25 ml). The solution was stirred at room temperature for 3 h, diluted with ice/water (20 ml) and the precipitate filtered off giving 1·83 g (84%) as white crystals, m.p. 185–187°C; [^{1}H]NMR δ 10·3*, 9·1* (2 × s, 2H), 7·8–7·6 (m, 4H), 7·0* (br s, 2H),

1·78, 1·80 (d, 6H); [^{13}C]NMR δ 155·1, 151·8, 141·9, 132·8, 128·7, 118·3, 24·6, 17·5; EI/MS *m/z*: 253 (M-$CONH_2$).

2.2.4.8 N-(p-*Ethylidenehydrazinosulfonylphenyl*)-N^1-*carbamoylurea* (***5h***). Prepared similarly to **5g**, using acetaldehyde (30 ml), 88% of a white powder, m.p. 170–171°C; [^{1}H]NMR δ 10·8*, 10·3*, (2 × s, 2H), 9·2* (s, 1H), 7·8–7·6 (m, 4H), 7·0* (br s, 2H), 6·8 (q, 1H), 1·75 (s, 3H).

2.2.4.9 N-(-p-(*2-Butylidenehydrazinosulfonyl*)*phenyl*)-N^1-*carbamoylurea* (***5i***). Similarly prepared using 2-butanone (20 ml), except that the mixture was initially warmed at 60° for 15 min, 73% of white crystals, m.p. 173–174°C; [^{1}H]NMR δ 10·4*, 10·1*, (2 × s, 2H), 9·1* (s, 1H), 7·7–7·5 (m, 4H), 6·8* (br s, 2H,), 2·4 (s, 3H), 2·1 (q, 2H), 0·95 (t, 3H).

2.2.4.10 N-(p-*Benzylidenehydrazinosulfonylphenyl*)-N^1-*carbamoylurea* (***5j***). Similarly prepared using benzaldehyde (10 ml) in THF (20 ml) with initial warming at 60° for 15 min, 49% of colourless crystals, m.p. 203–204°C; [^{1}H]NMR δ 11·4*, 10·3* (2 × s, 2H), 9·0* (s, 1H), 7·5–7·3 (m, 9H), 7·0* (br s, 2H).

2.2.4.11 N-(p-*Azidosulfonylphenyl*)-N^1-*carbamoylurea* (***5k***). A solution of compound the (2 g, 7·2 mmol) in acetone (50 ml) was gradually added to a stirred solution of sodium azide (1·4 g, 20 mmol) in water (30 ml). The suspension was stirred at room temperature for 4 h and poured on to ice/water (200 ml). The resultant precipitate was filtered off and recrystallised from aqueous acetone giving 1·88 g (90%), m.p. 181–182°C; IR υ_{max} 3320, 2050, 1340, 1166 cm^{-1}; [^{1}H]NMR δ 10·4*, 9·1* (2 × s, 2H), 7·8–7·6 (m, 4H), 7·0* (br s, 2H); [^{13}C]NMR δ 155·1, 151·8, 144·5, 130·3, 128·5, 119·1; EI/MS *m/z*: (M-$NHCONH_2$).

2.2.4.12 N-(p-*Trimethylphosphatiminosulfonylphenyl*)-N^1-*carbamoylurea* (***5l***). A solution of compound **5k** (1 g, 3·5 mmol) in toluene (50 ml) was reacted with trimethyl phosphite (0·52 g, 4·2 mmol). The mixture was warmed on the water bath for 40 min and cooled in an ice-bath. The precipitate was filtered off, washed with ether and dried giving 1·25 g (91%). m.p. 186–189°C; IR υ_{max} 3300, 1340, 1160 cm^{-1}; [^{1}H]NMR δ 10·3*, 9·15* (2 × s, 2H), 7·8–7·6 (m, 4H), 7·0* (br s, 2H), 3·7 (s, 9H); EI/MS *m/z*: 320 (M-$NHCONH_2$); FAB (+)/MS M/Z: 381 ($M^+ + 1$).

2.3 Biological assays

The compounds synthesised were tested *in vivo* for fungicidal activity against barley powdery mildew (*Erysiphe graminis* DC f. sp. *hordei* Marchal). The results were compared with those obtained from propiconazole and fenpropidin (two commercial fungicides used against powdery mildew in cereals).

2.3.1 Determination of fungicidal activity

Seeds of barley (*Hordeum vulgare* L cv. Golden Promise) were sown in Fison's Levington compost in 36-cm trays. Plants were grown in a greenhouse under natural daylight supplemented for 16 h per day by illumination with 400 W mercury vapour lamps. The maximum temperature during the day was 24°C falling to a minimum of 9°C at night. Plants at growth stage 12 (second leaf unfolded, Zadok's scale) were used for the experiments. The seedlings were sprayed to run-off with neutralised (pH 7) aqueous solutions of the test compounds (100 mg $litre^{-1}$) containing 'Tween' 20 (0·1 g $litre^{-1}$). Spraying was performed using a Sandon spray unit 3 days after inoculation with powdery mildew conidia achieved by shaking infected stock plants over the seedlings. The intensity of fungal infection was assessed 6, 7, 8, 10 and 12 days after inoculation by estimation of the percentage leaf area affected using a standard area diagram. All values for percentage leaf area infection measurements were $< \pm 15\%$. Barley powdery mildew normally sporulates six or seven days after inoculation. (Field rates for the standard compounds propiconazole and fenpropidin typically have concentrations of 420 mg $litre^{-1}$ and 2500 mg $litre^{-1}$ respectively).

3 RESULTS AND DISCUSSION

The antifungal activities of the *N*-(*p*-sulfonylphenyl)-N^1-carbamoylureas are given in Table 1, together with those for the two commercial fungicides propiconazole and fenpropidin. The activities are reported as the percentage activity in comparison with the control at various times after inoculation of barley seedlings with *Erysiphe graminis* Inspection of the data shows that all the compounds tested exhibited some antifungal properties and that the activity was considerably influenced by the nature of the sulfonyl substituent (R). In the sulfonamide derivatives (**5a**–**5d**), the 2,6-dimethylmorpholidate (**5d**) was much more fungicidal than the others and showed good retention of activity after 10 days. The enhanced activity shown by this compound in comparison with **5c** may be due to the presence of the dimethylmorpholino group which is well known to be associated with fungicidal properties.[5] (There are several important fungicides, e.g. dodemorph and tridemorph, which contain the 2,6-dimethylmorpholino moiety, and which are active against powdery mildews.)

Good fungitoxicity was also observed with the hydrazide derivative (**5f**) which is probably the result of in-vivo hydrolysis to free hydrazine within the fungus. The most active compound, however, was the acetone

hydrazone derivative (**5g**) which retained very high activity after 10 days. Its activity was certainly on a par with (if not better than) the activities of the commercial fungicides. The enhanced fungitoxicity exhibited by **5g** as compared with that shown by the parent hydrazide (**5f**) may be due to the acetone hydrazone (**5g**) possessing a more favourable oil/water partition coefficient allowing the substrate to move and readily penetrate the fungal cell. The least active compound examined was the trimethylphosphatiminosulfonyl derivative (**5l**).

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